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DNA-based immunization.

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Over the past 2 years the principle of nucleic acid immunization has been demonstrated in several different animal models. Each of these was based on direct gene transfer using plasmid DNA into one or more tissues, with skeletal muscle being the preferred target. The expression vectors used to date have encoded antigens from several different viruses as well as a tumor-specific protein, an MHC class I molecule and a parasite antigen. It is clear that the induction of a broad range of immune responses is possible with DNA-based immunization, including the ability to confer protection against viral or parasitic challenge. In some cases, the immune response is superior to that obtained with traditional recombinant protein vaccination. For example, in the case of hepatitis B surface antigen, antibody appears earlier and levels rise more quickly with DNA-based than with recombinant protein vaccination (Davis et al., 1994). Despite the very promising beginning of this new approach, many issues remain to be examined before application to humans, especially those concerned with safety. In the meantime however, DNA-based immunization offers an extremely powerful tool for molecular immunologists to study the immune system and with which to develop new vaccines and other immunotherapeutic approaches. One can easily and rapidly clone and modify genes in plasmid DNA expression vectors, allowing many new constructs to be produced and tested in a short period of time which can be on the order of weeks. In contrast, the preparation of viral vectors, or the production and purification of recombinant proteins from bacteria, yeast or stably transfected mammalian cell lines, can easily take months to develop. The DNA-mediated induction of an immune response to a protein produced in situ has therefore initiated a new era of vaccine research. There is now the possibility to dramatically modify the way

one approaches prophylactic vaccination, and as a consequence public health care can potentially be improved in a highly cost-effective manner.

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ARTICLES

Immunogenicity and antigenicity of the ATPase/helicase domain of the hepatitis C virus non-structural 3 protein

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The immunogenicity and antigenicity of an enzymatically functional (ATPase/helicase) recombinant protein encompassing residues 1207-1612 of the hepatitis C virus (HCV) non-structural 3 (NS3) protein was characterized using B10 congenic mice. Previous studies have indicated a high frequency of NS3-specific antibodies in HCV-infected humans. Similarly, all six immunized murine haplotypes were antibody responders to the NS3 ATPase/helicase domain, with the H-2k and H-2s haplotypes as high responders. As also observed in HCV-infected humans, the murine NS3 antibodies were predominantly directed to conformational determinants. Irrespective of the murine haplotype, IgG1 predominated in the primary anti-NS3 response, whereas IgG1 and IgG2b predominated in the secondary response. The antibody responder hierarchy was reiterated at the T cell level, with the H-2k and the H-2s haplotypes as the best responders. In both the H-2d and H-2k haplotypes ATPase/helicase-primed T cells secreted interleukin 2 and interferon gamma, corroborating observations from HCV-infected humans. In the H- 2d, H-2k and H-2s haplotypes the fine specificity of the T cell recognition of the ATPase/helicase domain was further characterized. Multiple, although generally weak, T cell recognition sites were found for all three haplotypes. The large size of the NS3 protein together with the presence of multiple class II binding motifs explain the high prevalence of NS3 antibodies in immunized mice and predict a similar explanation for the observed high frequency of NS3-specific antibodies in HCV-infected humans.

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